III. REMARKS/ARGUMENTS

Claims 1-8 and 11-25 are pending. Claims 1 and 11 have been amended. Applicants respectfully submit that no new matter has been added by virtue of this amendment.

A. Rejection over WO 89/09066

In the Office Action, the Examiner rejected claims 1-4, 6-8, 11-16 and 18-25 under 35 U.S.C. § 102 (b) as being anticipated by WO 89/09066 (hereinafter "the '066 reference"). The Examiner stated, *inter alia*, that the '066 reference "discloses a controlled release composition comprising an active agent, a polymeric matrix comprising a water-soluble polymer and a surface- active agent, for zero order release rate . . . " The Examiner further rejected claims 5 and 17 under 35 U.S.C. § 103 (a) as being unpatentable over the '066 reference and stated that the '066 reference "fails to teach the instant ratios of hydrophobic and hydrophilic components of matrix. However, . . . [it] teaches the compositions for zero order release rates of active agents and also teaches the claimed morphine compounds... [and] that the combination of surface-active agents and the polymer in the matrix enable the release of drug at a substantially constant rate. Therefore, it would have been within the scope of a skilled artisan at the time of the instant invention to optimize the amounts of surface-active agents and the soluble polymer ... such that a homogenous matrix is obtained which provides a zero order release rate of the active agent."

This reference is respectfully traversed. The present invention is directed to a formulation which provides the specified release rate over the first 8 hours in essentially zero order and a specified combination of Tmax and Cmax/C_{24} hour ratio. Such a formulation has advantages over prior art formulations in avoiding large peaks and troughs in plasma concentration.

It is respectfully submitted that the '066 reference neither teaches nor suggests a formulation which provides the combined features of releasing 15% to 45% of the drug load over 8 hours at a zero order date and has a $Cmax/C_{24}$ ratio of 1.5 to 3.5. These combined features of a relatively fast but steady release in the early period after administration and a low $Cmax/C_{24}$ ratio provides a flat, smooth plasma profile which avoids steep peaks and troughs which can be found with other controlled release preparations.

In support of this position, the following is a brief discussion of the examples of the '066 reference. It is noted that one skilled in the art would recognize that the term "zero order release" means a constant rate of drug release over a defined period of time, e.g., a formulation which releases 240 mg of drug over a 24 hour period according to a zero order release rate would have a rate of release of 10 mg/hr.

Example 1 is a composition dispersed in a pre-formed silicone tube and releases over at least 3 days at steady state. It would be impossible for only 45% or less of the active ingredient to have been released over 8 hours.

Example 2 is similar to Example 1 releasing over at least 8 days and the same distinction can be made.

Example 3 has a polyurethane tube rather than silicone and releases over at least 28 hours at a steady rate. The same distinction applies.

Example 4 has a pre-formed PTFE tube and release is over 10 hours. As the release was at a steady rate this means that 80% of the drug would be released at 8 hours.

Example 5 also uses a pre-formed teflon tube. The information appears to indicate that 100% of the drug is released in 8 hours.

Example 6 like Example 5, uses a pre-formed teflon tube and indicates release over 30 hours at a steady rate. Accordingly the release at 8 hours would be 27%. However, given that the release continues for 30 hours at a steady rate it can be deduced that a ratio of Cmax to C_{24} could not be in the range of 1.5 to 3.5.

Example 7 likewise uses a pre-formed teflon tube and release is at a steady rate over 8 days. This releases only about 4% of the active ingredient in 8 hours.

Example 8 again uses pre-formed teflon tubing. The release rate is at a steady 7 mg/hour over 24 hours. It cannot be conceived that if the preparation has been releasing right up to 24 hours at a steady state that a $Cmax/C_{24}$ hour ratio greater than 1 could be achieved.

Example 9 uses a pre-formed teflon tube. The erosion rate of the matrix is 6mm/24 hours but this does not say whether this was the tubal erosion or eriosion from one end only. In view of the lack of information no real comparison can be made with the present claims.

Example 10 (a) describes a polyurethane coated rod. It releases quickly and at 4 mm/hr from both ends the rod will be totally eroded after 1 1/4 hours. It cannot therefore give zero order release over 8 hours.

Example 10 (b) a formulation like 10(a), this releases quickly and will be totally eroded in about 3 hours.

Example 10 (c) a formulation like 10(a), this also releases quickly and will be totally eroded in about less than 4 hours.

Example 10 (d) a formulation like 10(a), this will erode in about 14.7 hours which, at steady state, means that over 50% of the product will be eroded in 8 hours.

Example 10 (e) This product was similar to that of 10 (a). The erosion rate was such that the product would be totally eroded in about 11 ½ hours, so that at a steady rate of erosion nearly 70% of the active will have been released in 8 hours.

Example 10 (f) This is similar to 10(e) but an even great percentage of the drug will have been released in 8 hours.

Example 10 (g) Considering the rate of erosion of the active ingredient-containing rod the total content of active is released in the 4 hours mentioned.

Example 10 (h) The total erosion of the active agent-containing rod is achieved in 10 hours. This at 8 hours 80% of the active will have been released; far greater than allowed in the present claim.

Example 10 (i) In this formulation the "active ingredient" tartrazin is apparently entirely released after 10 hours, meaning that at 8 hours over 60% of the "active" will have been released.

Example 10 (j) In this example no indication is given of the length of the rod containing sulcralfate. Therefore, this example is not an enabling disclosure and cannot be cited against the present claims.

Example 10 (k) This was prepared as in 10(a) which indicated a 10 mm rod. Assuming 2 mm erosion at each end over 8 hours, total erosion would be in about 16 hours with 50% release in 8 hours.

Example 10 (l) In this product the erosion rate at each end was 1.9 mm/hr meaning in all 3.8 mm/hr and is completely eroded after 4 hours.

Example 10 (m) In this case the rods were 3.5 mm long and eroded at 0.23 mm/hr meaning the total erosion was complete at 8 hours.

Example 11 In this Example with a release of 15 mg of theophyllin per hour 90% of the theophyllin is released in 8 hours. Looking also at the patient data the mean tmax is 7.6 hours, or 6.4 hours if the outlying patient 6 is discounted. These values are not within the claimed tmax range.

Example 12 In this Example the formulation unit dose is in the form of a rod which is either 15 mm or 30 mm long. The erosion rate is 1 mm/24 hrs so that the total dissolution time would be 15 days or 30 days, thus precluding a release of 15% to 45% of the active ingredient in 8 hours.

The Examiner has erroneously assumed that because certain of the excipients and active ingredients in the '066 reference are the same as can be used in the present invention, the dosage forms must inherently perform the same way. This is an unscientific analysis and fails to take into account the construction of the formulation, the release characteristics, and the pharmacokinetics of the '066 formulations. These parameters in the present claims are limiting features which distinguish the present invention from the cited reference.

With respect to dependent claims 5 and 6, the specification of the present invention discloses fatty acid esters as hydrophobic fusible materials and polyethylene glycol as a wicking agent. To the extent that the '066 reference overlaps with the materials of the present invention, the '066 reference describes fatty acid esters as surface active agents and polyethylene glycol as a polymer matrix. However, the '066 reference teaches that the maximum amount of surface active agent is 50% by weight of the polymer and the surface active agent (see page 8, lines 24-35). This is a ratio which is at the most, 1:1 (fatty acid ester:polyethylene glycol). In sharp contrast, when the present invention utilizes fatty acid esters and polyethylene glycol, the ratio of these components

is from about 8:1 to about 16:1. This correlates to a minimum of an 800% difference in the amount of fatty acid ester as compared to the '066 reference. It is respectfully submitted that the presently claimed ratio is not taught nor suggested by the '066 reference. In fact, the '066 reference teaches away from the present invention at page 9, lines 1-3 which states that "[i]f the surface active agent exceeds about 50%, there is a risk of phase inversion, whereby the surface active agent may become the continuous phase." Accordingly, the '066 reference doses not teach or suggest an 800% increase as compared to the presently claimed invention. Therefore, as suggested by the '066 reference, increasing the amount of surface active agent may have a negative effect on the operation of the purported invention described therein. On this note, the Examiner is respectfully reminded of the following:

> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious."

MPEP 2143.01, Eighth Edition, Incorporating Revision No. 1 (citing In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Therefore, it is respectfully submitted that the present invention is not taught nor suggested by the '066 reference.

C. Double Patenting Rejections

In the Office Action, claims 1-8 and 11-15 were rejected under the judicially created doctrine of obviousness type double patenting over claims 1-8 and 11-22 of U.S. Patent No. 6,399,096 and over claims 1-33 of U.S. Patent No. 5,965,163.

In response, Applicants respectfully submit the enclosed terminal disclaimer over U.S. Patent No. 6,399,096. Applicant notes that the obviation of an obvious-type double patenting rejection by the filing of a terminal disclaimer is not an admission, acquiescence, or estoppel on the merits of an issue of obviousness. See Quad Environmental Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 873-74, 20 U.S.P.Q.2d 1392, 1394-95 (Fed. Cir. 1991).

With respect U.S. Patent No. 5,965,163; it is respectfully submitted that at the very least, the zero order release of the present claims is not obvious in view of claims 1-33 of this patent and the Examiner is requested to remove these rejections.

D. Rejection Under 35 U.S.C. § 102 in View of U.S. 4,828,836 to Elger et al.

In the Office Action, the Examiner maintained her rejection of claims 1-4, 8, 11, 12, 14-16, and 24-25 under 35 U.S.C. § 102 (b) as being anticipated by U.S. 4,828,836 to Elger et al. (hereinafter "the Elger patent). The Examiner stated that "Elger does not state 'extrudate' or 'extrudate is directly incorporated into tablet or a capsule', as required by claim 1... However, the above limitations are related to the process of making the composition, and do not constitute a positive limitation." The Examiner further rejected claims 5 and 17 under 35 U.S.C. § 103 (a) as being unpatentable over Elger and stated that Elger "fails to teach the exactly same ratios as claimed . . . [however], optimizing the amounts of the hydrophobic and hydrophilic agents in the compositions of Elger so as to achieve a sustained release rate of a given active agent would have been obvious for one of an ordinary skill in the art." Initially, it is noted that the present claims are no longer limited to extruded dosage forms.

Applicants respectfully traverse this rejection. It is noted that this reference fails to teach any product which has a zero order release rate over the first eight hours. It can be readily observed from the in-vitro data in the Tables that the active ingredients are released in first order release profile, wherein the rate of release increases over time.

Further, one skilled in the art would not be motivated to modify the formulations of the Elger patent as the only clinical study disclosed therein (see columns 16/17) failed to provide a mean plasma concentration of the drug (theophylline), within therapeutic levels. It is noted that the generally accepted minimum therapeutic concentration of theophylline is 10 mg/l, more than three times the level reached in Elger.

Further, the Examiner compares the materials used in Elger to those disclosed in the present application and suggests that because similar agents are used, the formulation must inherently have the same release rates. The skilled person would know that the release rate can be adjusted by many factors, such as relative properties of ingredients, the manner in which they are put together, processing conditions and so forth. Therefore, it is improper to state that the formulations of Elger inherently possess the presently claimed parameters.

In support of this position, the Examiner is reminded that "[i]nherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present in the prior art." See *Trintec Industries Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597, 1599 (Fed. Cir. 2002) (*citing In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed Cir. 1999)). Further, "[i]nherency is established 'if the natural result flowing from the operation as taught would result in the performance of the questioned function . . . .'" *Scaltech Inc. v. Retec/Tetra LLC*, 60 USPQ2d 1687, 1692 (Fed. Cir. 2001) (*citing Continental Can Co. v. Monsanto Co.*, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)). It is respectfully submitted that claimed parameters as recited in claim 1 are not "necessarily present" in the Elger reference.

Further, it is respectfully submitted that the claimed parameters as recited in claim 1 are necessarily not present, as the Elger formulations do not exhibit essentially zero order release. Therefore, the Elger reference cannot inherently anticipate the present claims as they exhibit <u>different</u> parameters as recited in the present claims.

Accordingly, it is respectfully submitted that the Elger patent does not teach or suggest the present claims and the Examiner is requested to remove the rejections over this reference.

IV. Conclusion

In view of the actions taken and arguments presented, Applicants respectfully submit that the pending claims are in condition for allowance. An early and favorable Action on the merits is earnestly solicited.

It is believed that no fees are due for this submission. However, if it is determined that any fees are due or that any fee has been overpaid, the Commissioner for Patents is hereby authorized to charge said fees or credit any overpayment to Deposit Account No. 50-0552.

Respectfully submitted,
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